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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/480,389	01/11/2000	Bruce M. Boman	CATX-N	4258

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	26

DATE MAILED: 10/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/480,389	BOMAN, BRUCE M.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears n the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-28,32-35,37-44,55-57 and 59-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-28,32-35,37-44,55-57 and 59-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s) 22, 24, 25
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed May 23, 2003 was entered.

Claims 24-28, 32-35, 37-44, 55-57 and 59-61 are pending and examined on the merits.

2. The finality of the previous Office action is withdrawn in view of newly found references.

Claim Rejections Withdrawn:

3. The rejection of claims 24-28, 32-35, 37-44, 55-57 and 59-61 under 35 U.S.C. 112, first paragraph, for lack of enablement commenusurate with the scope of the specification is withdrawn upon further consideration and in view of the amendment.

4. The rejection of claims 24-28, 32-35, 37-43 and 58-60 under 35 U.S.C. 103(a) is withdrawn upon further consideration of the art.

5. The rejection of claims 24 and 44 under 35 U.S.C. 103(a) is withdrawn upon further consideration of the art.

Claim Rejections - 35 USC § 112

6. Claims 24-28, 32-35, 37-44, 55-57 and 59-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The basis for this rejection is that applicant not in possession of the claimed methods at the time of filing, because the disclosure fails to describe the genus of disease or disease-susceptibility traits that are "known" to be associated with a germline mutation that causes an about 50% decrease in the level of wild-type protein normally expressed by one of two or more subject genes.

The specification fails to provide an adequate description of the methods, because the specification fails to describe the criterion for "knowing" that a disease is associated with a germline mutation that causes an about 50% decrease in the level of wild-type protein. One criterion that is not addressed is when the knowledge is attained relative to the filing date of the application. Would diseases that fall within the category to be tested for using the claimed methods have to be known as of the filing date, or would diseases that were later established to known to be associated with a germline mutation that causes an about 50% decrease in level of wild-type protein also be included ? Another consideration for whether the specification has sufficiently described the genus of diseases that are "known" to be associated with a germline mutation that causes an about 50% decrease in the level of wild-type protein, is what constitutes "knowing". Is it merely the theoretical idea that loss of one allele, through gene-dosage effects,

will result in an about 50% decrease in the level of wild-type protein, or would one have to have actually measured protein levels and found this to be true ? This is an important question, because the specification only provides one example, the measurement of APC gene product, where data is shown, and contemplates all the other embodiments. Did applicant "know" at the time of filing that the other contemplated embodiments were those of diseases associated with a germline mutation that causes an about 50% decrease in level of wild-type protein because of the existence of protein-measurement data, or because of a reliance on the theory of gene-dosage effect on steady state protein levels ?

Furthermore, there is evidence that the mutations of genes contemplated by applicant at the time of filing, and specifically claimed as being included within the scope of the broadest claim 24, would not fit the criteria of being known to be associated with a disease through the process of producing an about 50% decrease in level of wild-type protein. Msh2 is one of the subject genes listed in claim 38, that is dependent from claim 24, and should therefore, be a gene, the germline mutation of which causes an about 50% decrease in level of wild-type protein. However, Bouffler (Bouffler, S.D. et al, British Journal of Cancer, 2000, 83: 1291-1294) teaches that Western blot analysis fails to detect a difference in Msh2 protein levels between wild type and heterozygote cells (see page 1292, 2nd col).

Additionally, the specification contemplates various subject genes that may be measured in the claimed methods, but fails to describe the antibodies that would be appropriate to make the measurements required for all of possible embodiments of the claimed methods. According to the teachings of the one exemplified embodiment, the choice of antibody appears to be critical to claimed methods. In the example where the APC gene product is detected, an antibody that

binds to a part of the protein that is lost through most of the different possible types of APC gene mutations is used for the detection of wild-type protein, and the specification teaches that the binding specificity of this antibody makes it a useful antibody in the claimed methods because this antibody will differentiate between wild-type and mutated APC proteins. Therefore, the lack of description of the antibodies required for differentiation between wild-type and mutated proteins renders the claimed methods inadequately described.

Claim Rejections - 35 USC § 103

Before setting forth the following rejections under 35 U.S.C 103(a), it is noted that the claimed inventions are drawn to methods of detecting disease or disease susceptibility traits, wherein the disease or disease susceptibility trait is "known" to be associated with a germline mutation that causes an about 50% decrease in the level of wild-type protein normally expressed by a subject gene. The claimed methods comprise detecting proteins immunologically and calculating a ratio of the amount of protein expressed from one subject gene in relation to the amount of protein expressed from another subject gene. For the broadest claims the two subject genes may be any gene, and therefore the ratio maybe the ratio of a protein product of a gene associated with cancer to the protein product of a gene that is not changed with cancer. Additionally, because the claims are drawn to detecting disease or disease susceptibility trait that is "known" to be associated with a germline mutation that causes an about 50% decrease in the level of wild-type protein normally expressed by a subject gene, it is assumed that the ratios measured would inherently reflect an about 50% percent decrease in normal level of wild-type

protein, especially in view of the broad scope of what is meant by "about 50%", which is defined to include 50% ± 20%, and which has not been defined with an upper and lower limit.

7. Claims 24-28, 32-35, 37, 39, 43, 55-57, 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vogelstein (U.S. 5,650,281; issued July 22, 1997; effective filing date Jan. 4, 1990) in view of Nozawa (U.S. Patent 5,328,826; issued July 12, 1994; filed March 23, 1992).

Vogelstein teaches methods for detecting germline mutations in a DCC gene comprising detecting loss of wild-type DCC gene by the detection of loss of expression products of the DCC gene, where the expression product may be a protein molecule, detected by Western blotting (see claims 20, 33 and 34; see also col. 9, lines 15-26, col. 6, lines 46-57).

Vogelstein differs from the claimed inventions by not explicitly stating how the detection of the protein expression product will be quantified, i.e. Vogelstein fails to teach measurements of a ratio of DCC protein to a second protein.

However, the use of a second protein that is believed to be unchanged in amount between test cells and control cells is known in the art. Nozawa teaches a method for the quantification of an endometrial cancer associated antigen by relating the measured amount of the endometrial associated antigen to the measured amount of a second protein (see col. 3, line 40 – col. 4, line 5; claim 1; col. 7, lines 24-36).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the claimed methods, because Vogelstein supplies the teaching that DCC gene product is lost or diminished in cancer, especially colorectal cancer and

because methods for specifically quantitating antigens of interest by relating the amount of the detected antigen to the amount of a second antigen is known in the art. Nozawa teaches the motivation for use of such quantification methods by describing many of the problems that may occur when attempting to associate the detection of an antigen with a disease state (see col. 1, line 32 – col. 3, line 39).

8. Claims 24-28, 32-35, 37-40, 43, 44, 55-57, 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Markowitz (U.S. 5,866,323; issued Feb. 2, 1999; effective filing date May 22, 1995) in view of Nozawa (U.S. Patent 5,328,826; issued July 12, 1994; filed March 23, 1992).

The specification appears to teach that TGF-beta RII gene is a gene that the germline mutation of which causes an about 50% decrease in the level of wild-type protein normally expressed by TGF-beta RII. Therefore, the measurement of TGF-beta RII protein levels should show a 50% decrease in those with a germline mutation compared to those without a germline mutation.

Markowitz teaches methods for detection of TGF-beta RII gene mutations by the detection of protein loss (see col 12, line 44 – col. 13, line 8). Markowitz does not explicitly teach that TGF beta RII may be a germline mutation, however, the specification teaches that this is a preferred subject gene for a method of detecting a disease associated with a germline mutation. Markowitz also differs from the claimed inventions by not explicitly stating how the detection of the protein expression product will be quantified, i.e. Markowitz fails to teach measurements of a ratio of TGF-beta RII protein to a second protein.

However, the use of a second protein that is believed to be unchanged in amount between test cells and control cells is known in the art. Nozawa teaches a method for the quantification of an endometrial cancer associated antigen by relating the measured amount of the endometrial associated antigen to the measured amount of a second protein (see col. 3, line 40 – col. 4, line 5; claim 1; col. 7, lines 24-36). Nozawa also teaches that the methods of protein detection using ratios may be automated (see col. 20, lines 54-59).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the claimed methods, because Markowitz supplies the teaching that the TGF-beta RII gene product is lost or diminished in cancer, especially colorectal cancer and because methods for specifically quantitating antigens of interest by relating the amount of the detected antigen to the amount of a second antigen is known in the art. Nozawa teaches the motivation for use of such quantification methods by describing many of the problems that may occur when attempting to associate the detection of an antigen with a disease state (see col. 1, line 32 – col. 3, line 39).

9. Claims 24-28, 32-35, 37-41, 43, 44, 55-57, 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liskay (U.S. 6,165,713; issued Dec. 26, 2000; effective filing date Dec. 9, 1994) in view of Nozawa (U.S. Patent 5,328,826; issued July 12, 1994; filed March 23, 1992).

The specification appears to teach that hMLH1 or hPMS1 are genes that the germline mutations of which cause an about 50% decrease in the level of wild-type protein normally expressed by either hMLH1 or hPMS1. Therefore, the measurement of hMLH1 or hPMS1

protein levels should show a 50% decrease in those with a germline mutation compared to those without a germline mutation.

Liskay teaches methods of diagnosing a DNA mismatch repair abnormality in a human subject, comprising detecting whether there is an abnormal deficiency of an hMLH1 or hPMS1 protein in a sample.

Liskay differs from the claimed inventions by not explicitly stating how the detection of the protein expression product will be quantified, i.e. Liskay fails to teach measurements of a ratio of either hMLH1 or hPMS1 protein to a second protein.

However, the use of a second protein that is believed to be unchanged in amount between test cells and control cells is known in the art. Nozawa teaches a method for the quantification of an endometrial cancer associated antigen by relating the measured amount of the endometrial associated antigen to the measured amount of a second protein (see col. 3, line 40 – col. 4, line 5; claim 1; col. 7, lines 24-36). Nozawa also teaches that the methods of protein detection using ratios may be automated (see col. 20, lines 54-59).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the claimed methods, because Liskay supplies the teaching that the hMLH1 or hPMS1 gene product is lost or diminished in cancer, and because methods for specifically quantitating antigens of interest by relating the amount of the detected antigen to the amount of a second antigen is known in the art. Nozawa teaches the motivation for use of such quantification methods by describing many of the problems that may occur when attempting to associate the detection of an antigen with a disease state (see col. 1, line 32 – col. 3, line 39).

10. Claims 24-28, 32-35, 37-40, 43, 44, 55-57, 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tavtigian (U.S. 6,124,104; issued Sep. 26, 2000; effective filing date Apr. 29, 1996) in view of Nozawa (U.S. Patent 5,328,826; issued July 12, 1994; filed March 23, 1992).

The specification appears to teach that BRCA2 gene is a gene that the germline mutation of which causes an about 50% decrease in the level of wild-type protein normally expressed by BRCA2. Therefore, the measurement of BRCA2 protein levels should show a 50% decrease in those with a germline mutation compared to those without a germline mutation.

Tavtigian teaches methods for detection of BRCA2 gene mutations by the detection of protein loss (see col 14, lines 52 – line 67; col. 15, line 61-col. 16, line 10; col. 53, lines 20-30). Tavtigian differs from the claimed inventions by not explicitly stating how the detection of the protein expression product will be quantified, i.e. Tavtigian fails to teach measurements of a ratio of BRCA2 protein to a second protein.

However, the use of a second protein that is believed to be unchanged in amount between test cells and control cells is known in the art. Nozawa teaches a method for the quantification of an endometrial cancer associated antigen by relating the measured amount of the endometrial associated antigen to the measured amount of a second protein (see col. 3, line 40 – col. 4, line 5; claim 1; col. 7, lines 24-36). Nozawa also teaches that the methods of protein detection using ratios may be automated (see col. 20, lines 54-59).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the claimed methods, because Tavtigian supplies the

teaching that the BRCA2 gene product is lost or diminished in cancer, especially breast cancer and because methods for specifically quantitating antigens of interest by relating the amount of the detected antigen to the amount of a second antigen is known in the art. Nozawa teaches the motivation for use of such quantification methods by describing many of the problems that may occur when attempting to associate the detection of an antigen with a disease state (see col. 1, line 32 – col. 3, line 39).

11. Claims 24-28, 32-35, 37-40, 43, 44, 55-57, 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albertsen (U.S. 6,413,727; issued Jul. 2, 2002; effective filing date Aug. 8, 1991) in view of Nozawa (U.S. Patent 5,328,826; issued July 12, 1994; filed March 23, 1992).

The specification appears to teach that APC gene is a gene that the germline mutation of which causes an about 50% decrease in the level of wild-type protein normally expressed by the APC gene. Therefore, the measurement of APC protein levels should show a 50% decrease in those with a germline mutation compared to those without a germline mutation.

Albertsen teaches methods for detection of APC gene mutations by the detection of protein loss (see col 5, lines 29-41; col. 7, lines 39-48; claims 3 and 4). Tavtigian differs from the claimed inventions by not explicitly stating how the detection of the protein expression product will be quantified, i.e. Tavtigian fails to teach measurements of a ratio of APC protein to a second protein.

However, the use of a second protein that is believed to be unchanged in amount between test cells and control cells is known in the art. Nozawa teaches a method for the quantification of an endometrial cancer associated antigen by relating the measured amount of the endometrial

associated antigen to the measured amount of a second protein (see col. 3, line 40 – col. 4, line 5; claim 1; col. 7, lines 24-36). Nozawa also teaches that the methods of protein detection using ratios may be automated (see col. 20, lines 54-59).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made the claimed methods, because Albertsen supplies the teaching that the APC gene product is lost or diminished in cancer, especially colorectal cancer and because methods for specifically quantitating antigens of interest by relating the amount of the detected antigen to the amount of a second antigen is known in the art. Nozawa teaches the motivation for use of such quantification methods by describing many of the problems that may occur when attempting to associate the detection of an antigen with a disease state (see col. 1, line 32 – col. 3, line 39).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
September 26, 2003

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